REMARKS

Claims 18-46 are pending in this applications. Claims 1-17 and 47-48 have been cancelled. Claims 18-46 are rejected. Claims 40, 41 and 43-46 are objected to.

Restriction to one invention was required under 35 U.S.C.§121. Applicants affirm the oral election made in the conversation with Kenneth Solomon on January 30, 2003. A provisional election was made without traverse to prosecute the invention of Group 1, claims 18-46. Accordingly, claims 1-17 and 47-48 have been canceled.

Claims 40-46 are objected to because they recite non-elected claims. Claims 40-46 have been amended to incorporate the subject matter of the non-elected claims. Claim 46 has also been amended to correct a typographical error. No new matter has been added as a result of these amendments. Accordingly, Applicants submit that the amended claims are in proper form and withdrawal of the objection to those claims is respectfully requested.

The disclosure is objected to because it contains an embedded hyperlink. The Applicants are required to delete the embedded hyperlink. The specification has been amended to delete the hyperlink.

The disclosure is also objected to because the specification recited GenBank accession numbers without providing the corresponding sequence identifiers. The reference has been deleted.

The change required at page 24, line 1, of the specification has been requested.

Accordingly, Applicants submit that the specification, as amended, is in proper form and withdrawal of the objections thereto are respectfully requested.

Claims 18-38 and 42-46 are rejected under 35 U.S.C.§112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey

to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 18, 40 and 41 have been amended to recite the structure disclosed on page 5 of the specification and in claim 2. It is submitted, therefore, that the claims are adequately supported by the specification, and are in accordance with 35 U.S.C. §112, first paragraph. The Examiner, at page 5 of the Office Action, has indicated that this amendment would obviate the subject rejection.

Claims 19-38 and 42-46 depend from claims 18 and 40, respectively, and therefore incorporate all of the subject matter therein. Accordingly, Applicants submit that claims 18-38, 40 and 42-46 are adequately described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Therefore, Applicants respectfully request that the rejection of claims 18-38, 40 and 42-46 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 18-46 are rejected under 35 U.S.C.§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

With regard to claims 18, 39 and 40, the Examiner argues that the recitation of "introducing" renders the claim indefinite because it is unclear as to whether or not picolinic acid actually contacts the conformationally changed protein. The Examiner has suggested changing the "introducing" step to "administering...to the animal." Claims 18, 39 and 40 have been so amended. The Action states further that the claims were indefinite as to outcome of the claimed process. Applicant is aware of no authority requiring recitation of the outcome of the process. Nevertheless, claims18, 39 and 40 have also been amended to recite the outcome; that is, that the claimed compounds are administered to an animal to prevent or reverse conformationally altered

protein assembly or aggregation in the animal. As such, it is submitted that claims 18-46 are definite under 35 U.S.C. §112, second paragraph.

With regard to claims 21 and 37 the Action states that the recitation of "biologically active subunit" is indefinite because the term "subunit" refers to one of folded protein chains that constitutes a quaternary protein, yet β-amyloid is a monomeric protein, not a protein having quaternary structure that is composed by subunits. As such, secondary to the Action, the recitation of "subunit of at least one protein selected from..." is indefinite. Applicant traverses the rejection.

Words in a claim must be given their plain meaning unless the Applicants have provided a clear definition in the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Here, the Examiner is applying the narrowest definition of the term "subunit" instead of the more broad definition provided in the specification. However, the Examiner must interpret the term in light of the definition provided in the specification, which is improper. The Examiner's attention is directed to the present specification, page 11, lines 5-20, where the phrase "biologically active subunit" is defined. In accordance with the present invention, a biologically active subunit is a subunit of a peptide, which has at least about 10% activity of a peptide of the invention. Using the definition provided in the specification, a monomeric protein can have subunits. The definition does not require that a protein with a quaternary structure. Accordingly, it is submitted that claims 21 and 37 are sufficiently definite under 35 U.S.C. § 112.

Claims 36-38 are rejected because they recite the phrase "containing at least one protein..." The Examiner argues that it is not apparent as to whether or not the metalloprotein is a fusion protein in which the metalloprotein is a part of the fusion or the metalloprotein forms a

complex with the protein having peptide sequence of one or SEQ ID NOS: 1-7. Claims 36-38 have been amended for clarification.

Claim 46 is rejected because it recites "treating conformational altered protein." The Examiner argues that the recitation does not make it clear as to how and by what the protein is treated. Claim 46 has been amended for clarification.

For all of the above reasons, Applicants respectfully request that the rejection of claims 18-46 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Applicants believe that the amendments and remarks set forth herein place the application in condition for allowance. If the application is not in condition for allowance, the Examiner is respectfully requested to contact the undersigned attorney by telephone.

Respectfully submitted,

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Enclosures: Pending Claims Sheet
Marked-up Claims Sheet
Replacement paragraph sheet
Marked-up copy of paragraphs sheet

cc: docketing
Avinash Amin (w/ encl.)

U.S. PATENT APPLICATION SERIAL NUMBER 09/904,987

MARKED-UP CLAIMS SHEET

1. (Cancelled)

2. (Cancelled)

3. (Cancelled)

4. (Cancelled)

5. (Cancelled)

6. (Cancelled)

7. (Cancelled)

8. (Cancelled)

9. (Cancelled)

10. (Cancelled)

11. (Cancelled)

12. (Cancelled)

13. (Cancelled)

14. (Cancelled)

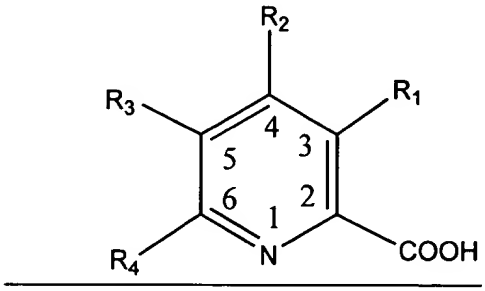
15. (Cancelled)

16. (Cancelled)

17. (Cancelled)

18. (Once Amended) A method of preventing or reversing conformationally altered protein assembly or aggregation in an animal, comprising:

[introducing picolinic acid, its analogs, or derivatives to the conformationally altered protein] <u>administering to the animal a compound of the following structure:</u>



wherein R_1, R_2, R_3 and R_4 are selected from a group consisting of an oligopeptide, carboxyl group, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, secondary butyl group, tertiary butyl group, pentyl group, isopentyl group, neopentyl group, fluorine, chlorine, bromine, iodine and hydrogen, thereby preventing or reversing conformationally altered protein assembly or aggregation.

19. (Once Amended) The method of claim 18, wherein [said step of introducing a derivative of picolinic acid comprises introducing fusaric acid to the conformationally altered protein] R_3 is a butyl group.

20. (Once Amended) The method of claim 18, [wherein the step of introducing picolinic acid, or its analogs or derivatives to the conformationally altered protein comprises introducing picolinic acid, its analogs, or derivatives to conformationally altered proteins,] wherein said conformationally altered protein is at least one protein selected from a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

21. (Once Amended) The method of claim 18, [wherein the step of introducing picolinic acid, or its analogs or derivatives to the conformationally altered protein comprises introducing picolinic acid, its analogs or derivatives to the conformationally altered protein,] wherein said protein contains a biologically active subunit of at least one protein selected from a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

22. (Once Amended) The method of claim 18, [wherein the step of introducing picolinic acid, or its analogs or derivatives to the conformationally altered protein comprises introducing picolinic acid, its analogs, or derivatives to the conformationally altered protein, comprises introducing picolinic acid, or its analogs or derivatives to said protein,] wherein said protein contains a biologically active variant of at least one protein selected from a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

23. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or derivations to the conformationally altered protein comprises introducing] picolinic acid, [its] analogs or derivatives, is administered to an animal by injection.

24. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or [derivations] derivatives, to the conformationally altered protein comprises introducing] picolinic acid, its analogs or derivatives, is administered to an animal orally.

25. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or derivations to the conformationally altered protein comprises introducing] picolinic acid, its analogs or derivatives, is administered to an animal buccally.

26. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or derivations to the conformationally altered protein comprises introducing] picolinic acid, its analogs or derivatives, is administered to an animal parenterally.

27. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or derivations to the conformationally altered protein comprises introducing] picolinic acid, its analogs or derivatives, is administered to an animal transdermally.

28. (Once Amended) The method of claim 27, wherein the [step of introducing picolinic acid, its analogs, or derivations to an animal transdermally comprises:] administration

comprises placing a permeable membrane in fluid communication with a solution comprising said picolinic acid, its analogs or derivatives, directly on the skin of said animal.

29. (Once Amended) The method of claim 27, wherein the step of administering picolinic acid, its analogs, or [derivations] derivatives to an animal transdermally is enhanced by methods selected from a group consisting of iontophoresis, phonophoresis and by chemical penetration enhancers selected from a group consisting of fatty acids, fatty alcohols and terpenes.

30. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or derivations to the conformationally altered protein comprises introducing] picolinic acid, its analogs or derivatives, is administered to [an] the animal rectally.

31. (Once Amended) The method of claim 30, [wherein said step of introducing picolinic acid, its analogs, or derivations to an animal rectally comprises] comprising administering a solution comprising picolinic acid, its analogs or derivatives, in combination with a glyceride, by suppository into the rectum of said animal.

32. (Once Amended) The method of claim 18, wherein the [step of introducing picolinic acid, its analogs, or derivations to the conformationally altered protein comprises introducing] picolinic acid, its analogs or derivatives, is administered as a depot preparation.

33. (Once Amended) The method of claim 32, [wherein said step of introducing picolinic acid, its analogs, or derivations as a depot preparation comprises] comprising administering [introducing] said picolinic acid, or an analog or derivative thereof by implantation or intramuscularly injecting a solution comprising picolinic acid, its analogs or derivatives, in combination with a polymeric or hydrophobic material.

34. (Once Amended) The method of claim 33, [wherein said step of introducing picolinic acid, its analogs, or derivatives comprises introducing] comprising administering said picolinic acid, its analogs, or derivatives by implantation or intramuscularly injecting a solution comprising picolinic acid, its analogs, or derivatives, in combination with a polymeric material,

wherein the polymeric material is at least one selected from a group consisting of an emulsion in an oil and an ion exchange resin.

35. (Once Amended) The method of claim 33, [wherein the step of introducing picolinic acid, its analogs, or derivatives comprises introducing] comprising administering said picolinic acid, its analogs, or derivatives by implantation or intramuscularly injecting a solution comprising picolinic acid, its analogs, or derivatives, in combination with a hydrophobic material, wherein the hydrophobic material is a sparingly soluble salt of a picolinic acid anion, analogs or derivatives thereof.

36. (Once Amended) The method of claim 18, further comprising disrupting a metalloprotein complexed with a transition metal ion [containing] and at least one protein sequence selected from a group consisting of SEQ ID NO:1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

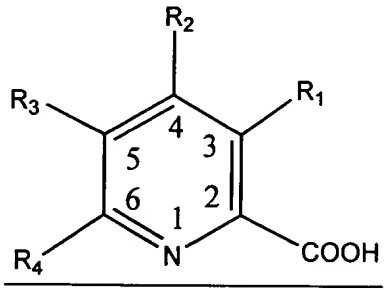
37. (Once Amended) The method of claim 18, further comprising disrupting a metalloprotein complexed with a transition metal ion [containing] and a biologically active subunit of at least one protein selected from a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

38. (Once Amended) The method of claim 18, further comprising disrupting a metalloprotein complexed with a transition metal ion [containing] and a biologically active variant of at least one protein selected from a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

39. (Once Amended) A method of preventing or reversing conformationally altered protein assembly or aggregation in an animal comprising administering to the animal a composition comprising [introducing] fusaric acid [to], thereby preventing or reversing [a] conformationally altered protein assembly or aggregation.

40. (Once Amended) A method of treating conformationally altered protein assembly or aggregation in an animal comprising:

administering to the animal a therapeutically effective amount of [the composition of claim 2] a compound represented by the following structure: [to said animal]



wherein R_1, R_2, R_3 and R_4 are selected from the group consisting of an oligopeptide, carboxyl group, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, secondary butyl group, tertiary butyl group, pentyl group, isopentyl group, neopentyl group, fluorine, chlorine, bromine, iodine and hydrogen, thereby preventing or reversing conformationally altered protein assembly or aggregation.

41. (Once Amended) [A] The method of claim 40 [treating conformationally altered protein assembly or aggregation in an animal comprising:

administering a therapeutically effective amount of the composition of claim 2 to said animal,] wherein R_3 [of said composition] is a butyl group.

42. (Once Amended) The method of claim 40, wherein the administration of said therapeutically effective amount of said composition [of claim 1] comprises:

administering said therapeutically effective amount of said composition to cells within said animal.

43. (Once Amended) The method of claim 42, wherein the administration of said therapeutically effective amount of said composition to cells comprises:

administering the composition [of claim 1] to cells which are within an animal selected from a group consisting of a human, a cow, a sheep, a deer and a goat.

44. (Once Amended) The method of claim 43, wherein the administration of said therapeutically effective amount of said composition to cells within a human comprises:

administering the composition [of claim 1] to brain tissue cells within said human.

45. (Once Amended) The method of claim 40, further comprising adding said therapeutically effective amount of said compound [of claim 1] to a treatment regimen of at least one or more therapeutic agents.

46. (Once Amended) The method of claim 40, wherein the [step of administering of said therapeutically effective amount of said compound of claim 1 further comprises treating conformational] <u>conformationally</u> altered [proteins] <u>protein assembly or aggregation is</u> caused by a disease selected from a group consisting of Alzheimer's disease, spongiform encephalopathy, cerebral amyloid angiopathy, Parkinson's disease, frontal temporal dementia, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease and Creutzfelds-Jakob disease.

47. (Cancelled)

48. (Cancelled)

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CLEAN COPY OF THE REPLACEMENT PARAGRAPHS

On page 8, line 25 through page 9, line 6:

FIG. 1 shows SEQ ID NO: 1, the polypeptide sequence of Beta-Amyloid (βA) as contained in Homo sapiens Beta-Amyloid Precursor Protein (APP_{770}) in GenBank Accession No. QRHUA4 from positions 672 to 714. The term "β -amyloid," "β -amyloid peptide" or "βA" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kDa, which peptide is substantially homologous to the form of the protein described by Glenner, *et al.* including mutations and post-translational modifications of the normal β-amyloid peptide (Glenner et al., *Biochem. Biophys. Res. Commun.* 120:885-890 (1984)), and comprising SEQ ID NO: 1, as well as biologically active variants of SEQ ID NO: 1, which has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, identity or homology to SEQ ID NO: 1 or a biologically active subunit thereof. Biologically active subunits of βA, biologically active variant βA polypeptides, and biologically active subunits thereof, falling within the scope of the invention, have at least about 50%, preferably at least about 80%, and more preferably at least about 90% the activity of the polypeptide comprising SEQ ID NO: 1.

On page 24 , line 1:

EXAMPLE 2 - REVERSAL OF βA AGGREGATION BY CHANGING PROTEIN CONFORMATION

On page 10, lines 4-13:

FIG. 5 shows SEQ ID NO: 5, the polypeptide sequence of Tau in Homo sapiens as listed in GenBank Accession No. NM016835. The term "Tau" refers to a 758 amino acid peptide having a molecular weight of about 78.9 kDa, comprising SEQ ID NO: 5 which has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, identity or homology to SEQ ID NO: 5 or a biologically active subunit thereof. Biologically active subunits of Tau, biologically active variant Tau polypeptides, and biologically active subunits thereof, falling within the scope of the invention, have at least about 50%, preferably at least

80%, and more preferably at least about 90% the activity of the polypeptide comprising SEQ ID NO: 5.

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MARKED-UP COPY OF THE REPLACEMENT PARAGRAPHS

On page 8, line 25 through page 9, line 6:

FIG. 1 shows SEQ ID NO: 1, the polypeptide sequence of Beta-Amyloid (βA) as contained in Homo sapiens Beta-Amyloid Precursor Protein (APP_{770}) in GenBank Accession No. QRHUA4 from positions 672 to 714[, available at http://www.ncbi.nlm.nih.gov, herein incorporated by reference in its entirety]. The term "β -amyloid," "β -amyloid peptide" or "βA" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kDa, which peptide is substantially homologous to the form of the protein described by Glenner, *et al.* including mutations and post-translational modifications of the normal β-amyloid peptide (Glenner et al., *Biochem. Biophys. Res. Commun.* 120:885-890 (1984)), and comprising SEQ ID NO: 1, as well as biologically active variants of SEQ ID NO: 1, which has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, identity or homology to SEQ ID NO: 1 or a biologically active subunit thereof. Biologically active subunits of βA, biologically active variant βA polypeptides, and biologically active subunits thereof, falling within the scope of the invention, have at least about 50%, preferably at least about 80%, and more preferably at least about 90% the activity of the polypeptide comprising SEQ ID NO: 1.

On page 24 , line 1:

EXAMPLE 2 - REVERSAL OF [BA] <u>βA</u> AGGREGATION BY CHANGING PROTEIN CONFORMATION

On page 10, lines 4-13:

FIG. 5 shows SEQ ID NO: 5, the polypeptide sequence of Tau in Homo sapiens as listed in GenBank Accession No. NM016835. The term "Tau" refers to a 758 amino acid peptide having a molecular weight of about 78.9 kDa, comprising SEQ ID NO: 5 which has at least about 80%, preferably at least about 90%, and more preferably at least about 95%, identity or homology to SEQ ID NO: 5 or a biologically active subunit thereof. Biologically active subunits of Tau, biologically active variant Tau polypeptides, and biologically active subunits

thereof, falling within the scope of the invention, have at least about 50%, preferably at least about 80%, and more preferably at least about 90% the activity of the polypeptide comprising SEQ ID NO: 5. [In particular, the biologically active variants of Tau can include peptides listed in GenBank at Accession Nos. NM_016841, NM_016834, and NM_005910.]